PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for azithromycin

This is a summary of the RMP for azithromycin. The RMP details important risks of azithromycin, how these risks can be minimised, and how more information will be obtained about azithromycin's risks and uncertainties (missing information).

Azithromycin's SmPC and its package leaflet give essential information to healthcare professionals and patients on how azithromycin should be used.

I. The Medicine and What It Is Used For

Azithromycin is authorised for the following indications:

Prolonged-release granules

- Acute bacterial exacerbations of chronic bronchitis
- Acute bacterial sinusitis
- Community-acquired pneumonia (CAP)
- Pharyngitis/tonsillitis caused by *Streptococcus pyogenes* in subjects intolerant to beta-lactam antimicrobials.

Other formulations

- lower respiratory tract infections including bronchitis and pneumonia
- odontostomatological infections
- skin and soft tissue infections
- acute otitis media
- upper respiratory tract infections including sinusitis and pharyngitis/tonsillitis
- sexually transmitted infections:
  - uncomplicated genital infections due to *Chlamydia trachomatis*
  - uncomplicated genital infections due to non-multiresistant *Neisseria gonorrhoeae*
  - chancroid due to *Haemophilus ducreyi*
- prophylaxis against *Mycobacterium avium intracellulare* complex (MAC) infection
- treatment of disseminated MAC infection in patients with advanced human immunodeficiency virus infection
- CAP (intravenous formulation only)
- pelvic inflammatory disease caused by susceptible organisms (*Chlamydia trachomatis, Neisseria gonorrhoeae, Mycoplasma hominis*) (intravenous formulation only).

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of azithromycin, together with measures to minimise such risks and the proposed studies for learning more about azithromycin's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals

- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the public (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about AEs is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of azithromycin is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of azithromycin are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of azithromycin. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

The MAH reclassified the important identified and potential risks detailed in Table 11 to risks that are "not considered important" for inclusion in the RMP, and therefore to remove them from the list of safety concerns. The MAH also reclassified the safety concerns detailed in Table 11 in missing information for removal.

Table 31. List of Important Risks and Missing Information

Important identified risks (PRF)	• None
Important identified risks (All formulations)	• QT prolongation/Torsade de pointes
Important potential risks (All formulations)	• None
Missing information	• None

PRF = prolonged-release granules formulation

II.B. Summary of Important Risks

Table 32. Important Identified Risk QT prolongation/Torsade de Pointes (All Formulations)

Evidence for linking the risk to the medicine	Recognised class effect for other macrolides, literature. Nonclinical studies (electrophysiological investigations) have shown a weak potential for QT prolongation. Reports of QT prolongation/TdP have been received during clinical development and in the post-marketing setting.
Risk factors and risk groups	Several risk factors of QT prolongation have been identified, such as female gender and structural heart disease. Other factors which may increase the risk of QT prolongation/Torsade de pointes include genetic predisposition (congenital long QT syndrome), age, and electrolyte disturbances (hypokalaemia, hypomagnesaemia).
Risk minimisation measures	Routine RMMs: the risk is communicated in SmPC section 4.4 (Special warnings and precautions for use) and Section 4.8 (Undesirable effects). No additional RMMs.
Additional pharmacovigilance activities	A0661209 (completed) A0661211 (ongoing)

RMM = risk minimisation measure; SmPC = summary of product characteristic; TdP = torsade de pointes

II.C. Post-Authorisation Development Plan

II.C.1. Studies which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of azithromycin.

II.C.2. Other Studies in Post-Authorisation Development Plan

There are no category 1–2 studies for azithromycin.[m] A0661211 is an ongoing category 3 study to examine effects of azithromycin use on cardiovascular (CV) mortality (safety concern: QT prolongation/TdP):

Study title: The acute effects of azithromycin use on cardiovascular mortality, as compared with amoxicillin-clavulanate in veterans.

Purpose of the study:
Primary objectives - To estimate hazard ratios (HRs) and risk differences (RDs) of CV death for azithromycin users as compared to amoxicillin-clavulanate users among persons 30-74 years of age within 10 days following the dispensed prescription, for a respiratory or ear-nose-throat (ENT) infection indication of use.:
Outcome: CV death
Subgroup analyses:

- CV death among those with a history of CV disease
- CV death among those with high baseline CV mortality risk as defined by a CV mortality risk score.

Secondary objectives - To estimate the HRs and RDs of non-CV death for azithromycin users as compared to amoxicillin-clavulanate users among persons 30-74 years of age within 10 days of dispensed prescription, for a respiratory or ENT infection indication of use:
Outcome: Non CV death
Subgroup analyses:

- Non-CV death among those with a history of CV disease.
- Non-CV death among those with high baseline CV mortality risk as defined by a CV mortality risk score.